April 22, 2004

Cynthia Graham, Ph.D.
Technical Contact
Bayer Corporation
100 Bayer Road
Pittsburgh, PA 15205

Dear Dr. Graham:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Benzyltrimethylammonium Chloride posted on the ChemRTK HPV Challenge Program Web site on December 17, 2003. I commend Bayer Corporation for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Bayer advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Benzyltrimethylammonium Chloride

Summary of EPA Comments

The sponsor, Bayer Chemicals LLC, submitted a test plan and robust summaries to EPA for benzyltrimethylammonium chloride (CAS No. 56-93-9) dated November 14, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on December 17, 2003.

EPA has reviewed this submission and reached the following conclusions:

1. Physicochemical Properties. The data are adequate for the purposes of the HPV Challenge Program.

2. Environmental Fate. The data are adequate for the purposes of the HPV Challenge Program. However, the submitter needs to provide a more basic discussion of stability in water and add the input values used to estimate fugacity in the respective robust summaries.

3. Health Effects. The acute, repeated-dose, genetic, and reproductive toxicity data are adequate for the purposes of the HPV Challenge Program. EPA agrees with the submitter that testing is needed for developmental toxicity. However, EPA recommends using the reproductive/developmental screening protocol OECD TG 421 rather than the developmental toxicity protocol OECD TG 414.

4. Ecological Effects. The acute toxicity data for invertebrates are adequate for the purposes of the HPV Challenge Program. However, the submitter needs to provide more information in the robust summary. The acute toxicity data for fish and algae are inadequate.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Benzyltrimethylammonium Chloride Challenge Submission

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data for melting point, boiling point, vapor pressure, and partition coefficient are adequate.

Water solubility. The submitter states that the chemical is highly water soluble and provides a value of >1 vol % at an unspecified temperature. The submitter needs to insert this value in the test plan summary table, or substitute an estimated value associated with a specific temperature.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation and biodegradation are adequate.

Stability in water. The submitter maintains that the chemical is very stable in water because its commercial form is a 60% aqueous solution. This information is insufficient to characterize stability in water because it does not address whether hydrolysis is possible in this case, although EPA agrees with the overall conclusion. The submitter needs to provide a brief technical discussion based on the resistance of the benzyltrimethylammonium cation to hydrolysis at environmental pH.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity

Submitted data for acute, repeated-dose, genetic, and reproductive toxicity are adequate.

Acute Toxicity. Acute toxicity data are technically inadequate because two of the studies were not designed to assess lethality, and they had post-dosing observation periods of ≤3 days (as opposed to the suggested 14 days). However, acute toxicity can also be deduced from repeated dose toxicity studies - see additional information on the NTP website in which the results of 16-day gavage studies in rats and mice are presented: http://ntp-server.niehs.nih.gov/htdocs/ST-studies/TOX057.html).

Developmental Toxicity. The submitter plans to conduct a developmental toxicity study following OECD TG 414. EPA suggests that the submitter consider using OECD TG 421 (reproductive/developmental toxicity screen protocol) based on the HPV Challenge Program policy for all new developmental toxicity studies (FR notice 65 81686-81698, December 26, 2000 - http://www.epa.gov/chemrtk/ts42213.pdf) unless other information suggests a different approach. The submitter needs to specify species and route of exposure.

Ecological Effects (fish, invertebrates, and algae)

Fish, Invertebrates, and Algae. The submitted test data for invertebrates are adequate. The submitted test data for algae are inadequate because the 14-day study duration is too long. The submitted ECOSAR-estimated data for fish (and the other aquatic species) are not adequate, as the submitter used the wrong ECOSAR model. The submitter may supply the correct ECOSAR estimate supported by data on an appropriate analog, or perform testing on fish using a study duration of 96 hours (OECD TG 203) and on algae using a study duration of 72 hours (OECD TG 201) or 96 hours (preferred; OPPTS TG 850.5400).

Specific Comments on the Robust Summaries

Environmental Fate

Fugacity. The submitter needs to incorporate the input values used in its model in the robust summary.

Health Effects

Acute Toxicity. The three robust summaries for acute oral toxicity do not specify group size (references 10 and 11), gavage vehicle, post-dosing observation period, mortality results by dose, and the method for calculating the LD_{50}.

Repeated-Dose Toxicity. The two robust summaries for the 13-week NTP gavage studies in rats and mice do not specify number of animals/sex/dose; incidence of neurological effects by dose; and histological effects, if any, on reproductive organs from control and high-dose animals.

Genetic Toxicity. The robust summary for a bacterial mutagenicity assay (reference 13) lacks information on whether cytotoxicity was observed, the criteria used for a positive result, and documentation that the positive and negative controls yielded appropriate responses. The robust summary for an in vitro chromosomal aberration assay (reference 13) does not specify the study year, the purity of the test material, the cytotoxic concentration, the number of metaphases examined/concentration, the criteria used for a positive result, and documentation that the positive and negative controls yielded appropriate responses.

Ecological Effects

Invertebrates. The robust summary for acute invertebrate toxicity does not clearly describe the test substance or its purity, and it does not identify the test guideline used. Also missing are study details such as concentrations tested, number of concentrations tested, number of animals/concentration, loading rate of the animals, control use/response, and mortality/toxicity signs/concentration. In addition, the endpoint is reported as both an EC_{50} value and an LC_{50} value in the summary and as an LC_{50} in the test plan.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.